REMARKS

Reconsideration and allowance are respectfully requested.

Claims 71-134 are pending. Rejoinder of withdrawn claims 71-89, 110-131 and 134 is requested upon allowance of an elected product claim.

An obvious typographical error is corrected in the present specification at page 7, which finds its counterpart in paragraph [0028] of the published US 2006/0014718. The degree of sulfation was inadvertently written as 4.26 instead of 4.35. Actually, 806 is the molecular weight (MW) of the epiK5-N,O-oversulfate from the sum of MW's for epiK5-N-sulfate (461 inclusive of sodium, sulfation degree of one) and the additional 3.35 sulfo groups (103 x 3.35 = 345.05 inclusive of sodium): i.e., 806 = 461 + 345. Furthermore, instead of providing the correct sulfation degree of the final product of Example 4 as determined by NMR (conferring a molecular weight of 806 to the disaccharide unit), the specification provided an underestimate determined by a conductimetric method (see the final part of Example 4), which is inconsistent with the calculated molecular weight of 806. Therefore, entry of the correction is requested.

Information Disclosure Statement

To satisfy their continuing duties of candor and good faith, Applicants bring to the attention of the Examiner related subject matter in Serial Nos. 09/738,879, 09/950,003, 10/240,606, 10/274,706, 10/484,883, 10/496,037, 10/518,229, 10/518,303, 10/582,687, 10/868,359, 10/902,285, 11/030,156, 11/440,749, 12/120,167 and 12/198,426. The Examiner is invited to consider their prosecution histories and the prior art of record in those applications, which are accessible through the PTO's Image File Wrapper (IFW), in view of the Federal Circuit's holding in *McKesson Information Solutions v. Bridge Medical*, 82 USPQ2d 1865 (Fed. Cir. 2007). To avoid duplication of those materials in the PTO's records, reference to the IFW is encouraged but Applicants would be ready to submit copies of these materials for the Examiner's review if she prefers.

Form PTO-1449 listing documents for the Examiner's consideration is attached; copies of the documents are also attached.

As provided by 37 CFR §§ 1.97(g) and (h), the Examiner should not infer that this information and the listed documents are prior art merely because they are submitted for consideration. Further, Applicants do not represent that the claimed subject matter was searched or that this statement encompasses all possible material information.

Consideration of the foregoing and attachments, as well as return of an initialed copy of Form PTO-1449 per M.P.E.P. § 609 to confirm the Examiner's consideration of this information are earnestly solicited.

35 U.S.C. 112 – Definiteness

Claims103 and 107 were rejected under Section 112, second paragraph, as allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse.

As regards the Examiner's interpretation of the term "LMW" on pages 4-5 of the Office Action, Applicants agree with her citation of the definition in the present specification and admit that this limitation means that LMW products are "low molecular weight products, obtained by fractionation or by depolymerization of K5-N-sulfate and consisting of or derived from K5-N-sulfates having a mean molecular weight from approximately 1,500 to approximately 12,000, calculated on a 100% N-sulfated product." They do not agree, however, that this definition limits LMW-epiK5-N,O-oversulfate to a molecular weight from approximately 1,500 to approximately 12,000.

The Examiner contended that there is an inconsistency between claim 103 drawn to LMW-epiK5-N,O-oversulfate having a mean molecular weight from approximately 2,000 to approximately 16,000 and the specification at page 7, which allegedly states that LMW means "from approximately 1,500 to approximately 12,000." But the latter quotation was incomplete as presented in the Office Action. The complete definition is quoted above. Because the claimed LMW-epiK5-N,O-oversulfate is *derived* from the epiK5-N-sulfate by introducing SO_3^- groups (each of molecular weight 103, inclusive of sodium), the larger range of molecular weights recited in claim 103 is perfectly compatible with the definition for K5-N-sulfates provided at page 7 of the present specification.

This compatibility is confirmed by the paragraph at the bottom of page 7, which explains that the molecular weight of the disaccharide unit, including the weight of the sodium, is "calculated as 461 in the case of an epiK5-N-sulfate-derivative and 806 in the case of an epiK5-N,O-oversulfated-derivative with a sulfation degree of 4.35" (emphasis added to highlight correction of the present specification). An epiK5-N-sulfate-derivative has a disaccharide unit with a molecular weight (MW) of 461 and a sulfation degree of one (the N-sulfate only), while an epiK5-N,O-oversulfate has a disaccharide unit with a MW that will depend on the number of sulfo groups introduced on the hydroxy groups, plus 1 (corresponding to the sulfo group reintroduced on the free amino group after the O-oversulfation): i.e., on the sulfation degree. Thus, an epiK5-N,O-oversulfate having a disaccharide unit of 806, inclusive of the weight of sodium will have a sulfation degree of 4.35. In fact, by adding the weight of 3.35 sulfo groups inclusive of sodium (103 x 3.35 = 345.05) to the MW of the disaccharide unit of the epiK5-N-sulfate (already containing one sulfo group), the sum obtained is 461 + 345.05 = 806.05, rounded down to 806.

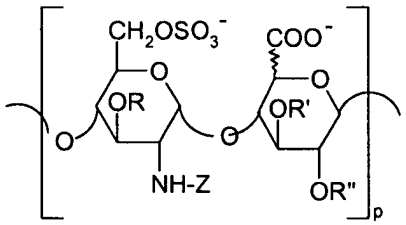
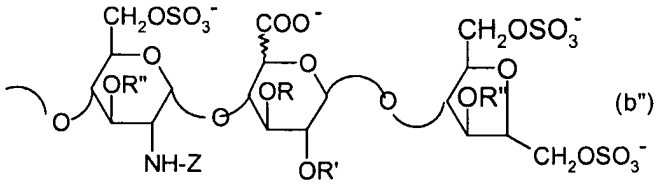
On the basis of the definitions given at page 7 of the specification, claim 103 is so precise that the skilled artisan is able to calculate the value of q in the formula III' for any sulfation degree. In fact, taking into account that there must be a sulfated uronic residue on the left of the structure in formula III' and a sulfated glucosamine (in the case of LMW products deriving from fractionated epiK5-N-sulfate) or 2,5-anhydromannitol (a') on the right of the structure (i.e., a supplemental disaccharide unit), claim 103 embraces LMW-epiK5-N,O-oversulfate having a mean molecular weight from approximately 2,000 to approximately 16,000 all included in formula III', wherein q is an integer from 2 to 20 for a sulfation degree from 4 to 5 as shown in the Table below.

Table

Sulfation Degree	Molecular Weight of Disaccharide (MWD)	Formula III' q + 1 =	
		MW 2,000	MW 16,000
4.00	461+309 = 770	2,000/770 = 2.60	16,000/770 = 20.78
4.26	461+335.8 = 796.8	2,000/796.8 = 2.51	16,000/796.8 = 20.08
4.35	461+345 = 806	2,000/806 = 2.48	16,000/806 = 19.85
4.60	461+370.8 = 831.8	2,000/831.8 = 2.40	16,000/831.8 = 19.23
5.00	461+412 = 873	2,000/873 = 2.29	16,000/873 = 18.33

Taking into account the definition of "approximately" on page 7 of the present specification, the mean molecular weights of the products of claim 103 are included in the value of q given in formula III' of claim 98.

The Examiner also contended that the dependency of claim 107 from claim 98, and the recitation of formula III'b in the former, allegedly causes claim 107 to contain moieties that are outside the definition in claim 98. In response, Applicants draw the Examiner's attention to their specification that specifically indicates that, for deploymerized LMW-epi-K5-N,O-oversulfates, the reducing end of the majority of the chains has the structure (b"), which the product of claim 107 has as well (see page 33, line 11, et seq. of the specification):

> Among these LMW-epiK5-N,O-oversulfates, are advantageous those consisting of a chain mixture in which the preponderant species has the formula III'a
>
> 
>
> (III'a)
>
> in which the uronic units are 20-60% consisting of iduronic acid, p is a integer from 4 to 8, Z is SO_3^-, R, R' and R" are hydrogen or SO_3^-, for a sulfation degree of at least 4, preferably from 4 to 4.6 and the corresponding cation is chemically or pharmaceutically acceptable.
> The origin of the new LMW-epiK5-amine-O-oversulfates from LMW-epiK5-sulfates obtained by nitrous depolymerization and subsequent reduction with, for example sodium borohydride, involves, at the reducing end of the majority of the chains in said chain mixture, the presence of a sulfated 2,5-anhydromannitol unit of structure (a') as shown above, in which R" represents hydrogen or SO_3^-.
> Thus, the reducing end of the majority of the chains in said chain mixture is represented by the structure (b")
>
> 
>
> (b")
>
> in which Z represents SO_3^- and the uronic unit can be glucuronic or iduronic.

As mentioned above, all the formulas given in Applicants' specification must have an (sulfated or unsulfated) uronic unit on the left of the structure and an (sulfated or unsulfated) glucosamine or 2,5-anhydromannitol unit on the right of the structure.

In the whole literature concerning heparin and, in general, glycosaminoglycans, each product is represented by the sole disaccharide unit, outside or within brackets (see, for example, the Casu and Leali documents cited in the obviousness rejections), being understood – and self-explanatory – to the skilled artisan that a non-reducing unit must be present on the left side and a reducing one must be present on the right side of the disaccharide, outside the brackets.

Claim 107 is perfectly clear to the skilled artisan, who would recognize that the subject matter of this claim is a depolymerized (see arrow on right at the bottom of page 5 of the Office Action) LMW-epiK5-N,O-oversulfate comprising m disaccharide units that must have a sulfated uronic unit (see arrow on left at the bottom of page 5 of the OA) on the left side of the structure. Therefore, the subject matter of claim 107 is a product consisting of a mixture of chains in which the preponderant species has the formula, III'b (i.e., consists of a chain mixture in which 100% of the chains have the formula III'b).

Applicants request withdrawal of the Section 112, second paragraph, rejection because the pending claims are clear and definite.

35 U.S.C. 103 – Nonobviousness

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by

the patent at issue"). The use of hindsight reasoning is impermissible. See id. at 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case under Section 103(a) requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396. An inquiry is required as to "whether the improvement is more than the predictable use of prior art elements according to their established functions." Id. at 1396. But a claim that is directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 90-109 and 132 were rejected under Section 103(a) as allegedly being unpatentable over Casu et al. (WO 98/42754) in view of Leali et al. (J. Biol. Chem. 276: 37900-37908, 2001). Applicants traverse because Casu's disclosure was not correctly interpreted in the Office Action.

On page 6 of the Office Action, it was alleged Casu teaches that LMW heparins have lower anticoagulant activity and better bioavailability as compared to traditional heparins. This is an incomplete and, thus, erroneous interpretation of the Casu's disclosure. As previously explained in the response to the first Office Action, the anti-Xa activity is an activity inhibiting Factor Xa of the coagulation cascade and, therefore, it represents an anticoagulant activity. One of ordinary skill in the art would know that, since the anti-Xa activity is an important index of anticoagulant activity (see, for example, Klein et al., Anesth. Analg. 91:1091-1095, 2000, where the authors clearly state, at page 1093, left column, last paragraph, that "the degree of factor Xa inhibition is directly related to its anticoagulation effect"), the statement in Casu concerning the lowered anticoagulant activity of the prior art, sulfated LMW heparin must refer to global anticoagulant activity, which is normally measured by the aPTT test (see also Barrowcliffe et al., J. Pharm. & Biomed. Anal., 7:217-226, 1989, in particular the Abstract, page 218, the first three lines, and page 219, the first seven lines; and Hemker et al., Thromb. Res. Suppl. 14:1-

10, 1991, in particular the Abstract, page 2, the first four lines of the chapter entitled "Specific and Global Activities" and page 3, lines 4-5).

In fact, all of Casu's products are antithrombotic agents. Casu's LMW heparins, which were cited by Examiner, though being less anticoagulant and more bioavailable than heparin must be anticoagulant and must be anticoagulant/antithrombotic because of their very high anti-Xa activity as unequivocally taught therein (see page 7, second line from bottom, and page 10, lines 20-21). Although Casu does not provide any result on the other component of antithrombotic activity (i.e., anti-IIa activity) or, in particular, the global anticoagulant activity, those activities must be present in the LMW heparin described therein albeit they might be less than those of heparin.

In contrast, the products of Applicants' claim 90 are neither anticoagulants nor antithrombotics (no activity on the coagulation or on the coagulation parameters, see page 9 and 10, first paragraph of both, and page 29, lines 7 and 8 from the bottom, of the present specification), but antiviral agents useful in the preparation of medicaments and pharmaceutical compositions (see page 35 of the present specification).

Therefore, the citation of Casu under Section 103(a) is improper because it does not disclose products practically inactive for coagulation parameters. Conversely, its disclosure supports the nonobviousness of Applicants' claimed products. In fact, according to Casu, one of ordinary skill in the art would have reasonably expected to obtain epimerized derivatives having anticoagulant and/or antithrombotic properties, but this is not the case for Applicants' claimed products.

As far as Leali is concerned, the product described therein and those taught by Applicants are completely different. It is not so easily (and, especially, immediately) possible, as it appears to be predicted in the Office Action, to replace a non-epimerized product with an epimerized product as evidenced by Applicants' specification. In addition, as set forth herein above, one of ordinary skill in the art would not have had a reasonable expectation to obtain antiviral agents having the epimerized structure of heparin-like products because such products would have been expected to have anticoagulant/antithrombotic activity. An antiviral agent having anticoagulant/antithrombotic properties would be useless.

Pinna et al. (Antimicrob. Agents Chemother. 52:3078-3084, 2008) describe a very high antiviral activity for the product of Example 4 on herpes simplex virus (HSV). Table 1 at page 3079 compares K5-N,OS(H) (Leali's product) and epiK5-N,OS(H) (the product of Example 4), wherein (H) means "highly sulfated". Figure 2B shows that both epimerized and non-epimerized oversulfated (H) K5 derivatives strongly inhibit HSV, in contrast to the corresponding sulfated derivatives having a lower (L) content of sulfate groups. This confirms what was already taught in Applicants' specification at page 35.

Therefore, starting from an epimerized product, one of ordinary skill in the art would not have reasonably expected to find (a) an oversulfated product devoid of activity for coagulation parameters (e.g., anti-Xa activity) and (b) the oversulfated product has antiviral activity, in particular against HSV.

Claims 90-109 and 132-133 were also rejected under Section 103(a) as allegedly being unpatentable over Casu et al. (WO 98/42754) in view of Leali et al. (J. Biol. Chem. 276:37900-37908, 2001), further in view of Oreste et al. (US 2002/0062019). Applicants traverse because the failure of Casu and Leali to disclose their claimed invention is not remedied by the attempt to combine their disclosures with Oreste.

Withdrawal of the Section 103 rejections is requested because the claims would not have been obvious to one of ordinary skill in the art when this invention was made.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if additional information is required.

Respectfully submitted,

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